DATA EVALUATION RECORD

DICAMBA

STUDY TYPE: 28-DAY INHALATION TOXICITY – RAT
(OCSPP 870.3465)

MRID 49461101

Prepared for
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Task Order No. 6-117

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DATA EVALUATION RECORD

STUDY TYPE: 28-Day Inhalation Toxicity - Rat OCSPP 870.3465.

PC CODE: 029801 **DP BARCODE:** None

TEST MATERIAL (PURITY): Dicamba (93.9%)

SYNONYMS: Dicamba Technical, BAS 183 H, 3,6-dichloro-2-methoxybenzoic acid; CL 58893; 183H.

CITATION: Ma-Hock, et al. (2014). BAS 183 H (Dicamba Technical): Repeated dose 28-day inhalation toxicity study in Wistar rats, dust. BASF SE, Experimental Toxicology and Ecology, Germany. Project No.: 4010267, August 28, 2014. MRID 49461101. Unpublished.

SPONSOR: BASF SE (Germany).

EXECUTIVE SUMMARY: In a nose-only inhalation toxicity study (MRID 49461101), four groups of Crl:WI(Han) rats (10/sex/group; ~7 weeks of age) were administered BAS 183 H [93.9% (Batch No. 0002B01BA-251)] as a dust aerosol at exposure concentrations of 0, 0.001, 0.005, or 0.050 mg/L for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on food consumption, hematology, clinical chemistry, or during ophthalmological examinations. Body weight was not adversely affected.. At 0.05 mg/L, lung weight was statistically increased in both sexes, and the following lung histological lesions were increased in incidence (# affected/10 in treated vs controls) in both sexes: (i) minimal to slight alveolar histiocytosis (10 vs 4 in males; 10 vs 1 in females); (ii) minimal macrophage aggregates (6 vs 0 in males; 8 vs 0 in females); (iii) minimal to slight bronchial hypertrophy/hyperplasia (10 vs 0 in males and females); and (iv) minimal to slight bronchiole-alveolar hyperplasia (8 vs 0 in males [only minimal]; 9 vs 0 in females). Additionally, one female had a few macrophage aggregates in the bronchus-associated lymphoid tissue. No adverse, treatment-related finding was noted at 0.001 or 0.005 mg/L.

The LOAEL in male Wistar rats was 0.050 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in the lung, and 0.050 mg/L in females based on multiple microscopic findings in the lung and associated lymph nodes. The NOAEL was 0.005 mg/L in males and 0.005 mg/L in females.

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: BAS 183 H

Description:	White solid
Lot/batch #:	0002B01BA-251
Purity:	93.9% a.i.
CAS # of TGAI:	1918-00-9
Structure:	[INCLUDEPICTURE "http://chem.sis.nlm.nih.gov/chemidplus/structure/1918-00-9" * MERGEFORMATINET]

2. Vehicle: Charcoal and HEPA filtered air.

3. Test animals:

Species:	Rat
Strain:	Crl:WI(Han)
Age/weight at study initiation:	~9 weeks/ Males = 224-263 g; Females = 168-198 g
Source:	Charles River Laboratories, Inc., Sulzfeld, Germany
Housing:	Five per polysulfonate cage with dust-free wooden bedding
Diet:	Kliba maintenance diet, Provimi Kliba SA, *ad libitum* except during exposure
Water:	Tap water, *ad libitum* except during exposure
Environmental conditions:	**Temperature:** 20-24 °C; 21.4-22.9 °C during exposure **Humidity:** 30-70%; 35.2-48.7% during exposure **Air changes:** 15/hour; 67/hour during exposure **Photoperiod:** 12 hours light/dark
Acclimation period:	About 10 days; 3 days to exposure system

B. STUDY DESIGN:

1. **In life dates:** Start: March 27, 2014; End: April 24, 2014

2. **Animal assignment and treatment:** Rats were randomly assigned by computer to experimental groups based upon body weights not varying by more than ±20% of the mean (Table 1). Concentrations were selected for the 28-day study by the Sponsor. No details were provided.

TABLE 1. Study Design				
Experimental parameter	Exposure concentrations (mg/L)			
	Group 0 0	Group 1 0.001	Group 2 0.005	Group 3 0.050
Number of Rats				
Total no. of animals assigned	20 (10/sex)	20 (10/sex)	20 (10/sex)	20 (10/sex)
Sacrifice and necropsy	20 (10/sex)	20 (10/sex)	20 (10/sex)	20 (10/sex)
Behavioral testing (FOB, Motor Activity)	Not done in this study			
Blood cholinesterase determination	Not done in this study			
Measured Concentration				
Achieved aerosol concen. (mg/L ± s.d.)	NA	0.00094±0.00001[a]	0.0050±0.00008[a]	0.0493±0.0055[a]
Achieved chemical concen. (mg/L)	NA	0.00092	0.00501	0.0471

Data obtained from pages 22, 43, & 48 (MRID 49461101)
[a] MMADs were within the Guideline recommended range of 1-3 µm.

3. **Generation of the test atmosphere / chamber description:** The test material was desagglomerated with a household mixer (Braun, type MX32), sieved in a screening machine (250 µm mesh; Prufsieb JEL 200), and the resulting powder mixed with 1% Aerosil 200 to increase its flowability. Chamber atmospheres were generated using solid particle brush generators (BASF SE, Germany) coupled with mixing chambers, cyclonic separators (BASF SE, Germany), and a distribution system that delivered controlled amounts of dust aerosol and filtered compressed air to the inlet of each 90 L nose-only exposure chamber (INA 60, BASF SE, Germany). Nose-only exposure chambers (one for each exposure level) were fitted with air flow meters, pressure gauges, and other devices to measure temperature, humidity, and test article concentration. The animals were acclimatized to the restraining devices for three days prior to the commencement of exposures.

4. **Test atmosphere concentration:** The exposure concentrations in each exposure chamber were measured real-time using scattered light photometers (Vis-Guard) and gravimetrically three times per day (2/day for the low concentration). Samples were taken from the breathing zone of the animals using preweighed filters. Results are in Table 1 and show that the achieved mean test substance concentrations were 94, 100, and 99% of target values for the low, mid, and high exposure concentrations, respectively. Homogeneity of concentrations and any rotation of animals was not addressed. Time to equilibrium was not reported.

5. **Particle size determination:** Particle size for each exposure concentration was determined once weekly during the study using Marple 298 stack samplers (New Star Environmental, Rosswell, GA). The mass median aerodynamic diameter (MMAD) and geometric standard deviation (σg) ranges were 1.8-2.2 µm (1.7-1.9), 1.7-1.9 µm (1.8-2.1), and 1.7-2.1 µm (1.8-1.9) for the low, mid, and high concentration groups, respectively.

6. **Statistics:** Each test substance-exposed group was compared to the control group by sex. The overall minimum level of significance for intergroup differences was $p \leq 0.05$, except when noted otherwise. Body weight and body weight change were analyzed using Dunnett's test (two-sided). Nonparametric data (blood parameters) were analyzed using the one-sided Kruskal-Wallis test followed by pairwise comparisons using the Wilcoxon test (two-sided). Absolute and relative organ weights were analyzed using the two-sided Kruskal-Wallis test followed by pairwise comparisons using the Wilcoxon test (two-sided) for the hypothesis of equal medians.

C. METHODS / OBSERVATIONS:

1. **Mortality and clinical observations:** Animals were observed for abnormal behavior, mortality and morbidity twice daily and once on weekends and holidays. Detailed clinical observations were not conducted.

2. **Body weight:** Animals were weighed prior to exposure, on test day 0 (first administration of exposure), and twice weekly thereafter.

3. **Food consumption:** The amount of food consumed was estimated for each animal by cage and was recorded weekly. Feed efficiency was not calculated.

4. **Cholinesterase determination:** Cholinesterase activity was not measured.

5. **Ophthalmoscopic examination:** Eyes of rats from all experimental groups were dilated with a mydriatic agent and examined by an ophthalmoscope prior to the first day of exposure, and eyes of rats from the control and high dose groups were examined at the end of the study.

6. **Plasma concentration of the test substance:** Blood from the retro-orbital sinus was collected from all animals (non-fasted) on day 21 while under isoflurane anesthesia, and the plasma separated and frozen for later analysis of the test substance using reverse phase HPLC coupled with electrospray mass spectrometry.

7. **Hematology and clinical chemistry:** Blood was collected for hematology and clinical chemistry from all surviving animals at the end of the experimental period; the animals were fasted overnight prior to blood collection. Blood was collected from the retro-orbital sinus while the rats were under isoflurane anesthesia. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase*	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	Bile acids
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

8. **Urinalysis:** Not conducted.

9. **Sacrifice and pathology:** At study termination, all surviving rats were euthanized by exsanguination while under pentobarbital anesthesia and necropsied. Any gross lesions were recorded. Tissues from animals in all exposure groups were processed for microscopic evaluation. Microscopic examination was conducted on all tissues from the control and high exposure groups, while teeth, trachea, pharynx, larynx, liver, nasal cavities, lymph nodes, and lung were examined for all animals. A portion of lung from selected male animals (one control, two mid concentration, one high concentration) was examined for elastic and collagen fibers by a combination of Hart and modified Masson-Goldner staining. Selection criteria for this staining were not provided. The following CHECKED (X) tissues were collected. The (XX) organs were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+	X	GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+	X	OTHER
	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*		Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin
X	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+	X	Harderian gland
XX	Lung*	X	Mammary gland*	X	Teeth
X	Nasal cavity* (4 levels)				
X	Pharynx*				
X	Larynx*				

* Recommended for subchronic rodent studies based on Guideline 870.3465
+ Organ weights required

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs and mortality:** There were no mortalities or clinical signs observed at any exposure concentration.

B. BODY WEIGHT AND BODY WEIGHT GAIN: Selected body weight data are presented in Table 2. No significant effect was observed on body weight of either sex during the study. Cumulative weight gain of males at the high concentration was statistically lower (-40%; $p \leq 0.05$) for the 0-28 day interval. The lower weight gain in males at the high concentration was more pronounced during the second half of the study. No other significant body weight effects were observed.

TABLE 2. Body weight and body weight gain

Observation	Exposure concentration (mg/L)			
	0	0.001	0.005	0.050
Body weight-males (g ± s.d.)				
Day 0	247 ± 9.3	248 ± 12.2	243 ± 12.8	249 ± 9.4
Day 5	257 ± 9.2	261 ± 15.6	253 ± 14.7	260 ± 11.0
Day 12	265 ± 12.2	269 ± 16.1	260 ± 16.6	265 ± 14.7
Day 28	282 ± 16.5	285 ± 20.1	276 ± 22.0	270 ± 17.1
Body weight-females (g ± s.d.)				
Day 0	182 ± 7.8	185 ± 5.8	180 ± 8.8	184 ± 9.3
Day 4	186 ± 7.3	190 ± 10.2	182 ± 13.4	187 ± 10.1
Day 11	193 ± 9.9	196 ± 7.6	190 ± 7.5	194 ± 10.4
Day 28	202 ± 9.9	207 ± 8.5	200 ± 11.6	201 ± 12.1
Body weight gain-males (g)				
Days 0-5	10	13 (+30)	10(0)	11 (+10)
Days 0-12	18	21 (+17)	17(-6)	16 (-11)
Days 0-28	35	37 (+6)	33(-6)	21* (-40)
Body weight gain-females (g)				
Days 0-4	4	5 (+25)	2(-50)	3 (-25)
Days 0-11	11	11 (0)	10(+10)	10 (-10)
Days 0-28	20	22 (+10)	20(0)	17 (-15)

Data obtained from pages 71-74 (MRID 49461101).
Values in ( ) are % difference from controls.
* $p<0.05$
N = 10

C. **FOOD CONSUMPTION:** No statistics on individual food consumption were possible. Somewhat lower food consumption relative to controls was observed in both males (-9 to -18%) and females (-5 to -9%) at the high exposure throughout the study. This effect on food consumption did not result in biologically-relevant, decreased body weight and was not considered adverse.

D. **BLOOD ANALYSES:**

1. **Hematology:** No exposure-related effects were observed in the hematology data.

2. **Clinical chemistry:** Globulin, total protein, and calcium concentrations were significantly decreased ($p\leq0.01$; calcium $p\leq0.05$) in females at the mid- and high exposure levels, but these values were within historical control ranges (historical data provided). Also, the globulin and protein values of female controls were high compared to historical controls.

3. **Plasma concentration of the test substance:** Table 3 shows the plasma concentrations of the test substance after 21 days of exposure. The plasma concentration of BAS 183 H increased with exposure concentration, but not proportionally to the 5-fold and 10-fold step increases in exposure. The respective mean values of female animals were higher than those of the males.

TABLE 3. Plasma concentrations of BAS 183 H.

Target concentration BAS 183 H (Dicamba techn.) (mg/m³)	Mean plasma concentration of BAS 183 H (Dicamba techn.) (ng/mL)	
	Male (n = 10)	Female (n = 10)
1	36.9 ± 9.7	90.2 ± 34.6
5	129.5 ± 85.2	344.5 ± 120.9
50	1303.0 ± 578.7	2221.0 ± 1060.0

Data obtained from pages 52 (MRID 49461101).

E. OPHTHALMOSCOPIC EXAMINATION: No treatment-related lesions were observed during the ophthalmoscopic examinations.

F. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** No treatment-related macroscopic changes were observed in any tissues.

2. **Organ weight:** Selected organ weight data are shown in Table 4. The data show a statistically increased lung weight in both sexes at the high exposure concentration ($p \leq 0.05$). Histologic correlates were observed to these findings in the lung. Spleen weight (absolute only) was significantly decreased at the high exposure in males (0.467 g vs. 0.517 g for control; $p \leq 0.05$), but was not considered adverse due to lack of corroborating evidence of an effect on the spleen.

TABLE 4. Selected organ weight data.

Organ	Dietary concentration (mg/L)			
	0	0.001	0.005	0.050
Males				
Lung				
Absolute (g)	0.977 ± 0.131	1.008 ± 0.123	0.949 ± 0.059	1.133* ± 0.151
Relative-to-body wgt. (%)	0.383 ± 0.035	0.393 ± 0.05	0.382 ± 0.025	0.46** ± 0.057
Females				
Lung				
Absolute (g)	0.753 ± 0.065	0.762 ± 0.068	0.781 ± 0.092	0.882** ± 0.04
Relative-to-body wgt. (%)	0.422 ± 0.033	0.416 ± 0.037	0.446 ± 0.027	0.492** ± 0.027

* $p<0.05$; ** $p<0.01$
Data obtained from pages 173-203 (MRID 49461101).

3. **Microscopic pathology:** In the nasal cavity, a minimal increase/ hypertrophy of mucous cells was observed in the nasopharyngeal duct (Level IV) in 4/10 males and 6/10 females in the high concentration group. This finding was considered an adaptive response, since the epithelium in the affected areas was regular and there were no inflammatory or degenerative responses.

   The incidences of lesions in the larynx are shown in Table 5. A focal epithelial alteration of cuboidal cells at the base of the epiglottis (Level I) was observed in one control male and in most males and many females in the three BAS 183 H exposure groups (minimal at the low- and mid-concentrations; minimal to slight at the high concentration). The epithelial alteration

was characterized by a slight focal flattening of epithelial cells. One male in the high concentration group showed a minimal squamous cell metaplasia in the same area. The investigators considered these lesions to be treatment-related, but not adverse, quoting Kaufmann et al. (2009): "a treatment-related increased incidence of focal epithelial alteration as well as a minimal to slight laryngeal squamous metaplasia should be considered as non-adverse, as this is a frequent spontaneous change without dysfunction of the larynx".

TABLE 5. Incidence of larynx lesions

Larynx, level I	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1)	2 (5)	3 (50)	0 (0)	1 (1)	2 (5)	3 (50)
No. of animals	10	10	10	10	10	10	10	10
Epithelial alteration	1	10	9	8	0	6	5	9
• Grade 1	1	10	9	6		6	5	7
• Grade 2				2				2
Metaplasia, squamous				1				
• Grade 1				1				

Grade 1 = minimal; Grade 2 = slight
Data obtained from page 56 (MRID 49461101).

The incidences of treatment-related lesions in the lung are shown in Table 6. Minimal to slight alveolar histiocytosis (focal accumulation of some solitary alveolar macrophages) was increased in all males and females at the high concentration (minimal in 4/10 control males and 1/10 control females). A few macrophage aggregates (clusters of alveolar macrophages) were observed in six males and eight females at the high concentration. All males and females from the high concentration group showed a minimal to slight hypertrophy/ hyperplasia of the epithelium of single bronchi, bronchioles, or terminal bronchioles. Minimal or slight multifocal bronchiole-alveolar hyperplasia was seen in 2/10 and 8/10 males, respectively, in the mid- and high exposure groups. Nine females in the high exposure group also had this hyperplasia. One female at the high concentration had a few macrophage aggregates in the bronchus-associated lymphoid tissue (BALT). No elastic or collagen fibers were detected in the special stain testing of lung tissue from selected animals.

TABLE 6. Incidence of lung lesions

Lungs	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1)	2 (5)	3 (50)	0 (0)	1 (1)	2 (5)	3 (50)
No. of animals	10	10	10	10	10	10	10	10
Histiocytosis, alveolar	4	1	1	10	1	1	0	10
• Grade 1	4	1	1	5	1	1		8
• Grade 2				5				2
Macrophage aggregates	0	0	0	6	0	0	0	8
• Grade 1				6				8
Hypertr./ hyperpl. bronch.	0	0	0	10	0	0	0	10
• Grade 1				6				8
• Grade 2				4				2
Hyperplasia, bronch.-alv.	0	0	2	8	0	0	0	9
• Grade 1			2	8				8
• Grade 2								1
BALT; Macrophage aggregates	0	0	0	0	0	0	0	1
• Grade 1								1

Grade 1 = minimal; Grade 2 = slight
Hypertr./hyperpl. = hypertrophy/hyperplasia
BALT = bronchus-associated lymphoid tissue.
Data obtained from page 56 (MRID 49461101).

Associated with the effects observed in the lung were findings in the mediastinal and tracheobronchial lymph nodes (Table 7). Minimal to slight lymphoreticulocellular hyperplasia of the mediastinal lymph nodes was observed in both males and females at the high exposure concentration. In addition, minimal to moderate macrophage aggregates were observed in the mediastinal and tracheobronchial lymph nodes of both sexes at the high concentration.

TABLE 7. Incidence of lymph node lesions

Mediastinal lnn.	**Male animals**				**Female animals**			
Test group (mg/m³)	0 (0)	1 (1)	2 (5)	3 (50)	0 (0)	1 (1)	2 (5)	3 (50)
No. of animals	10	10	10	10	10	10	10	10
Hyperplasia, lympho-reticul.	0	0	0	3	0	0	0	3
• Grade 1				1				2
• Grade 2				2				1
Macrophage aggregates	0	0	0	5	0	0	0	5
• Grade 1				2				3
• Grade 2				2				2
• Grade 3				1				

Tracheobronch. lnn	**Male animals**				**Female animals**			
Test group (mg/m³)	0 (0)	1 (1)	2 (5)	3 (50)	0 (0)	1 (1)	2 (5)	3 (50)
No. of animals	10	10	9	10	9	9	10	10
Macrophage aggregates	0	0	0	5	0	0	0	4
• Grade 1				3				2
• Grade 2				2				
• Grade 3								2

Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate
Data obtained from page 57 (MRID 49461101).

III. DISCUSSION AND CONCLUSIONS:

A. <u>INVESTIGATORS' CONCLUSIONS</u>: The inhalation exposure of rats to BAS 183 H for 28 days caused no substance related adverse findings regarding clinical signs, body weight, ophthalmological examinations, food consumption, as well as clinical pathology parameters in blood. Histopathology examinations showed the following morphological changes in lungs of both sexes that were considered treatment-related and adverse: 1) minimal to slight hypertrophy/hyperplasia of bronchial epithelium observed at the high exposure concentration, and 2) minimal or slight multifocal bronchiole-alveolar hyperplasia observed at the mid- and high exposure concentrations. Other findings were considered treatment-related but not adverse. Specifically excluded was the focal epithelial alteration of cuboidal cells at the base of the epiglottis observed at an increased incidence at all three BAS 183 H exposure levels (Kaufmann et al., 2009). The no-observed-adverse-effect-level (NOAEL) was 0.001 mg/L for portal of entry effects on the lung and 0.050 mg/L for systemic toxicity.

B. REVIEWER COMMENTS:

No adverse, treatment-related findings were noted on clinical signs, body weight, ophthalmological examinations, food consumption, clinical chemistry, or hematology. No adverse, treatment-related finding was noted at 0.001 or 0.005 mg/L.

A treatment-related increased incidence of focal epithelial alteration was noted in both sexes at all concentrations (minimal at 0.001 and 0.005 mg/L; minimal to slight at 0.05 mg/L; 8-10/10 treated males vs 1/10 controls; 5-9/10 treated females vs 0/10 controls), and minimal laryngeal squamous metaplasia was noted in one 0.05 mg/L males. Due to the specific findings noted and the lack of severity, the Agency agrees with the conclusion of Kaufmann et al. (2009) that these findings should be considered as non-adverse, as this is a frequent spontaneous change without dysfunction of the larynx.

At 0.005 mg/L, an increased incidence of minimal bronchiole-alveolar hyperplasia was noted in males only (2/10 treated vs 0/10 controls). Due to the slight magnitude of increase in incidence, minimal severity, and lack of corroborating evidence of an adverse lung effect, this finding was not considered adverse at this dose level.

The LOAEL in male Wistar rats was 0.050 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in the lung, and 0.050 mg/L in females based on multiple microscopic findings in the lung and associated lymph nodes. The NOAEL was 0.005 mg/L in males and 0.005 mg/L in females.

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

C. STUDY DEFICIENCIES: None.

IV. REFERENCES

Kaufmann W, Bader R, Ernst H, Harada T, Hardisty J, Kittel B, Kolling A, Pino M, Renne R, Rittinghausen S, Schulte A, Wohrmann T, and M Rosenbruch. (2009). First International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment. Exp. Toxicol. Pathol. 61: 591-603.